J. Physiol. (1982), **332**, *pp.* 1–24
With 1 *plate and* 16 *text figures*
Printed in Great Britain

REVIEW LECTURE*

CENTRAL CHEMOSENSITIVITY AND THE REACTION THEORY

BY H. H. LOESCHCKE†

From the Institut für Physiologie, Ruhr-Universität Bochum, 4630 Bochum-Querenburg, Federal Republic of Germany

(*Received 15 December 1981*)

The aim of this discussion is to elucidate as much as possible the stimulus driving ventilation and the adaptation of this drive to the metabolic needs as well as its role in maintaining the acid–base balance of the brain. The main questions are: what is the adequate stimulus, where is the receptor, what is the mechanism of stimulation and what are the conditions in the surrounding of the receptor?

After a period when CO_2 and O_2 (or lack of O_2) were considered as the chemical stimuli, Winterstein (1911) proposed a unifying theory assuming that P_{O_2} and P_{CO_2} act on a single receptor by a single mechanism; he assumed the common denominator to be the hydrogen ion, either dissociated from carbonic acid or from other acids formed during oxygen deficiency.

In his reformulation of the reaction theory Winterstein (1956) accepted that there were two kinds of chemoreceptors, peripheral and central, which had to be considered separately. The part of Winterstein's theory which concerns oxygen and CO_2 in the peripheral chemoreceptors is still controversial though the sites of the hypoxia sensitive receptor have now been identified in the carotid and aortic glomera.

For the central chemoreceptor which is not sensitive to hypoxia (except what might be called modulations by P_{O_2}) the question is restricted to the alternatives that hydrogen ion or molecular CO_2 is the adequate stimulus. How difficult this is to answer becomes clear when the dramatic effect of inhaled CO_2 on ventilation is compared to the relatively small effect of administration of fixed acid. This discrepancy did indeed suggest a specificity of CO_2 (Nielsen, 1936). Much effort was necessary to show that this argument did not hold but an explicit refutation was not possible before the feed-back control system was better understood (Loeschcke, 1973).

The quantitative investigation of the blood components and their action on ventilation led to the general conclusion that the three possible stimuli P_{CO_2}, P_{O_2} and pH contributed their individual partial effects to the ventilatory drive. This multiple factor theory (Gray, 1950), however, while it served as a pragmatic approach, giving good predictions, was not conclusive as far as the stimuli were concerned because they were not measured at the *site of action on the receptor.*

* Text prepared by Professor H. H. Loeschcke for 1981 Annual Review Lecture of the Physiological Society. Unfortunately, owing to illness Professor Loeschcke was unable to deliver the lecture in person.

† Present address: Erich Heckelweg 8, D-7766 Gaienhofen, Federal Republic of Germany.

The reaction theory of central chemosensitivity

Starting in the early 1950s information was gathered concerning the location of the central chemosensitivity and generalizations will be avoided until this topic has been discussed. These studies of the effects of CO_2 and $[H^+]$ on ventilation became feasible when techniques were developed to perfuse the subarachnoid spaces (Leusen,

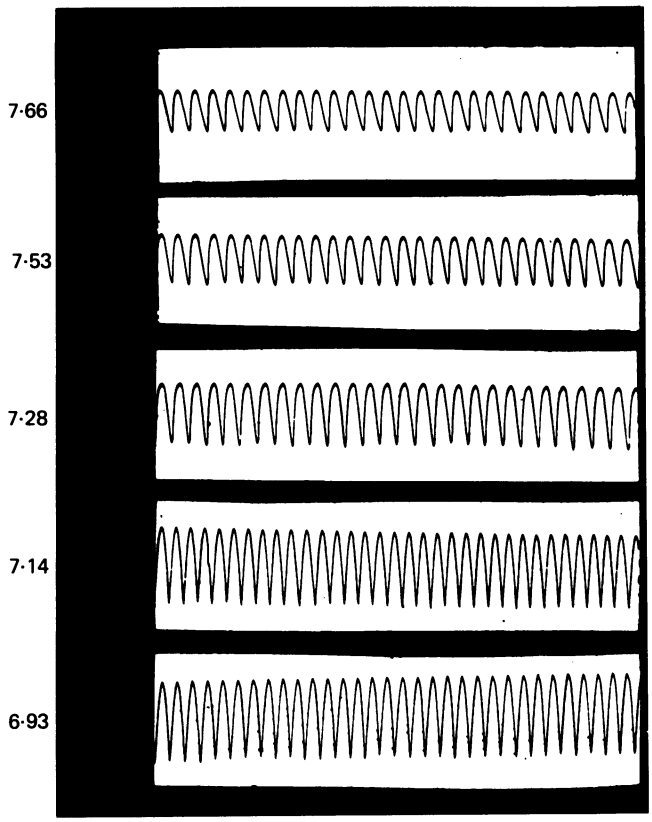


Fig. 1. Ventiliation during perfusion of the fourth ventricle and subarachnoid space with perfusates at different pH. P_{CO_2} was kept constant. Anaesthetized cat. Loeschcke *et al.* (1958). Courtesy of Springer-Verlag.

1954*a*, *b*). Loeschcke, Koepchen & Gertz (1958) used such experiments to differentiate between $[H^+]$ and P_{CO_2} by perfusion either with solutions with constant P_{CO_2} and varied pH (Fig. 1) or with constant pH and varied P_{CO_2}. Since P_{CO_2} at constant pH had if anything a depressing effect, while pH changes at constant P_{CO_2} drove ventilation, this excluded CO_2 as a stimulus in an experiment like this. Of course in the Henderson–Hasselbalch equation there are three variables pH, P_{CO_2} and $[HCO_3^-]$. Constancy of one factor necessarily confines the possibility of variation to the other two. This must still be considered a shortcoming of the argument, but acceptance of $[H^+]$ as *the* stimulus may be justified on the ground of 'economy of thinking'.

The observations were confirmed and extended by Mitchell, Loeschcke, Massion & Severinghaus (1963*a*) and Mitchell, Loeschcke, Severinghaus, Richardson & Massion (1963*b*) in the cat, Fencl, Miller & Pappenheimer (1966) and Pappenheimer (1967) in the goat and dog, and Hori, Roth & Yamamoto (1970) in the rat. The conlusions stayed the same. Both Pappenheimer (1967) and Loeschcke (1969) concluded that if there is a unique receptor to H^+ there must be a way to propagate the chemical signal in both respiratory and in metabolic acidosis so that the effects of the two types of acidosis may be explained quantitatively. Of course the contribution of the peripheral chemoreceptors must also be considered. This contribution in the steady state, however, is small.

Not all investigators were able to confirm these findings. Cragg, Patterson & Purves (1977) did not see increases of ventilation when applying acid to the ventral side of the medulla. It must, however, be stated that the experiment is not easy. The operation has to be done in such a way that there is not the slightest bleeding either on opening the dura and arachnoidea or during the entire course of the experiment; bleeding may lead to a sometimes invisible deposition of fibrin on the medulla which diminishes or abolishes the response. Also the anaesthesia has to be light; barbiturates in particular depress or abolish central chemosensitivity. This is usually not recognized on the first glance when the respiratory drive from peripheral chemoreceptors is intact, but it has been known for a long time (Benzinger, Opitz & Schoedel, 1938; Åström, 1952) that the sensitivity to inhaled CO_2 is very easily anaesthetized. The temperature, osmolality and calcium concentration of the perfusing fluids must of course be carefully maintained.

Until the mid-1970s pH was measured in the outflow of the perfusion or superfusion fluids and while Pappenheimer's group used ventricular perfusions, in our group superfusion of the ventral medullary surface was adopted. Recently pH was successfully measured either with micro-electrodes in the tissue of the medulla oblongata (Cragg *et al.* 1977) or with macro-electrodes on the surface of the medulla Ahmad, Berndt & Loeschcke, 1976; Shams, 1981).

The latter technique is based on the observation that there is free access to the glass electrode from the intercellular compartment. This is demonstrated by the free entry of horseradish peroxidase (Pl. 1) from the subarachnoid into the intercellular spaces (Dermietzel, 1976). The former technique (Cragg *et al.* 1977) has the advantage that the electrode is in the tissue, and the latter (Ahmad *et al.* 1976) that it is non-invasive. Cragg *et al.* (1977) were able to answer the old question (Lambertsen, Semple, Smith & Gelfand, 1961) as to whether the time courses of the pH in the medullary tissue and of ventilation during CO_2 inhalation are compatible. The answer was in the affirmative, indicating that the electrode indeed measures a pH which is representative of the stimulus.

Ahmad & Loeschcke (1982*a*) obtained, with the technique using surface macro-electrodes, the same result as had Cragg *et al.* (1977): the time courses of ventilation and of brain extracellular pH (pH_e) immediately following step-changes of inspired CO_2 were similar, showing little or no hysteresis. The tidal volume, especially after denervation of the peripheral chemoreceptors, followed closely the pH, measured on the surface of the medulla (Ahmad & Loeschcke, 1982*a*). In contrast, V_T and pH_e measured on the surface of the cortex, were unrelated (Fig. 2).

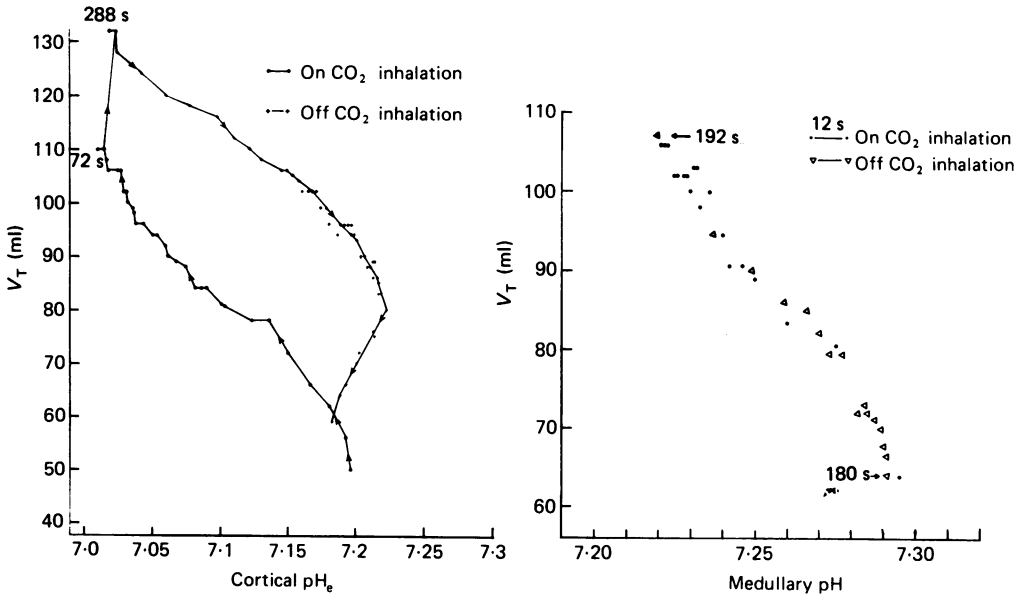


Fig. 2. Transients of V_T plotted against extracellular pH on the cortex (left) and on the medullary surface (right), during step changes of end-tidal P_{CO_2}. Points plotted are 12 s apart. On and off transients fall approximately on the same line for the medulla, while for the cortex there is a marked hysteresis loop. Ahmad & Loeschcke (1982*a*).

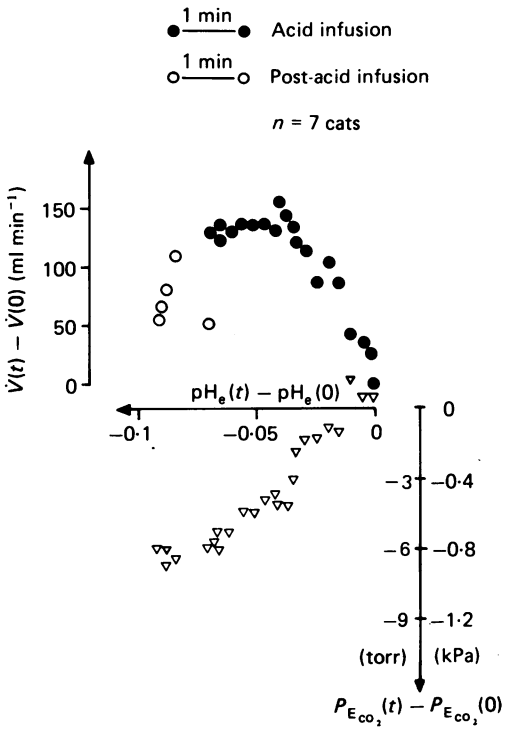


Fig. 3. Change of $\dot{V}$ (circles) and end-tidal P_{CO_2} (triangles) plotted against changes of pH measured on the medullary surface during infusion of H_2SO_4. The increase of $\dot{V}$ is reversed at higher degrees of acidosis. The plotted points are 1 min apart. Averages from experiments in seven cats. Shams *et al.* (unpublished).

Shams, Ahmad & Loeschcke (1981) injected acids intravenously, either HCl or H_2SO_4. The latter is not commonly used for inducing a metabolic acidosis. It is, however, better tolerated than HCl and in particular there is less depression of the arterial pressure. The acid–base effects are the same.

Shams' results came partly as a surprise. After acid injection with small changes of brain extracellular pH there was a steep response of ventilation and of tidal volume,

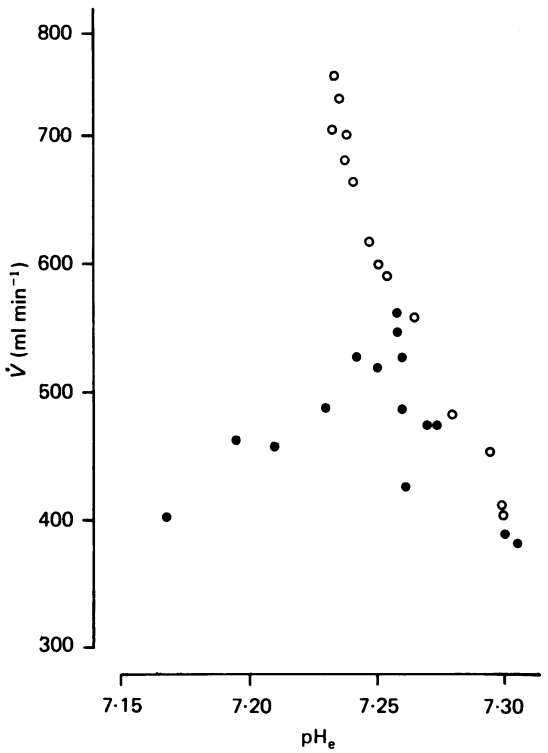


Fig. 4. Ventilation plotted against medullary surface pH in respiratory and metabolic acidosis. Metabolic acidosis (●) was introduced by acid infusion and respiratory acidosis (○) in a separate experiment by CO_2 inhalation. Up to a certain level there is a complete concordance of the responses to the two types of acidosis. Above this level the effect of metabolic acidosis is reversed while the response to CO_2 inhalation continues with undiminished slope. After Shams *et al.* (1981).

and this response was the same as the response to pH when CO_2 was inhaled. So far this is in full agreement with the hypothesis that metabolic and respiratory responses are mediated by the same receptor. The high gain accounts for the stability of extracellular pH under the experimental condition, as observed by Loeschcke & Sugioka (1969).

With the injection of *more acid*, however, ventilation and tidal volume unexpectedly ceased to rise and in most cases even dropped back towards control values (Fig. 3). In contrast, when the first injection of acid was followed by CO_2 inhalation rather than further injection of fixed acid, the ventilatory response to pH_e continued upwards with approximately the same slope (Fig. 4). When CO_2 was inhaled starting from different degrees of metabolic acidosis, response curves to pH_e of unchanged high

slope were obtained (Fig. 5). The position of the response curves was merely shifted to an increasingly acid pH_e. This indicates a different response to pH_e in metabolic and in respiratory acidosis. If the injection of acid is repeated after an interval, i.e. starting with a diminished pH_e, the response of ventilation to acid is again effective and again the reversal is observed.

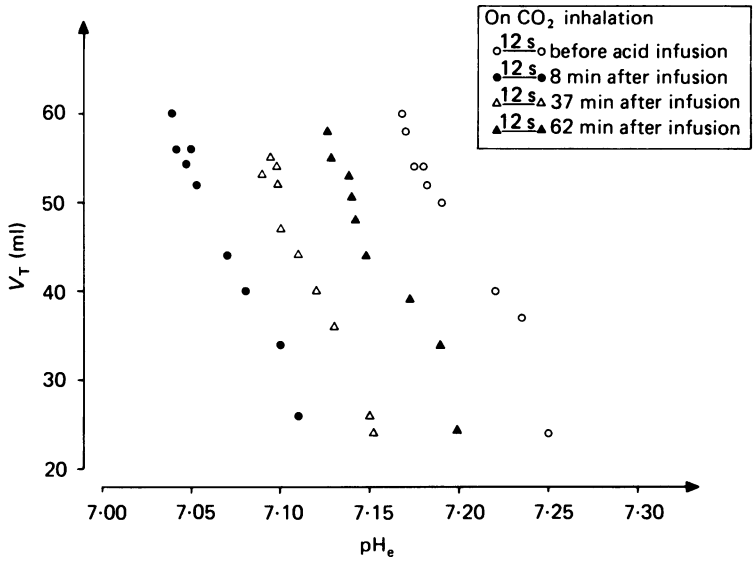


Fig. 5. Responses of V_T to medullary pH during inhalation of CO_2 initiated at different pH levels obtained by prior injection of fixed acid. The slopes of the responses remain unchanged (Shams *et al.* (unpublished)).

The interpretation of these findings is difficult but tentatively it may be speculated that the H^+ receptor after a certain level of response has been reached becomes inaccessible to further influx of H^+. It may be assumed that the sensing mechanism resides in a compartment which is initially accessible to H^+, but under the continued application of acid further entrance of H^+ is prevented; the lipid soluble acid, CO_2, penetrates as before. A synaptic gap for example, would be a good model (Fig. 6). As will be discussed later, quite different experiments do suggest an effect of H^+ on a synapse.

The drop of tidal volume at increasing $[H^+]$ after the critical response has been passed remains unexplained. Fukuda & Loeschcke (1977) showed the same kind of response in the neuronal activity. One of the possibilities to be discussed involves presynaptic inhibition.

As a result of this discussion it may be postulated that H^+ rather than CO_2 must be considered to be the adequate stimulus to central chemosensitivity. The system behaves as if stimulated by extracellular $[H^+]$ in metabolic as well as in respiratory acidosis. A modification of this postulate, however, seems to be necessary to account for the differences of metabolic and respiratory acidotic effects when higher doses of acid are injected. It is suggested that extracellular H^+ has free access to the H^+ receptor at mild degree of acidosis, but is prevented from reaching it in severe

metabolic acidosis, while the passage of CO_2 is uninhibited. A synaptic gap may tentatively serve as a model.

Localization and neurophysiology of central chemosensitivity

By applying pledgets of tissue paper soaked with acid or alkali (Mitchell *et al.* 1963*a*, *b*) or by superfusion of small spots of the ventral medullary surface (Schlaefke, See & Loeschcke, 1970) it was found that chemosensitivity was not uniformly

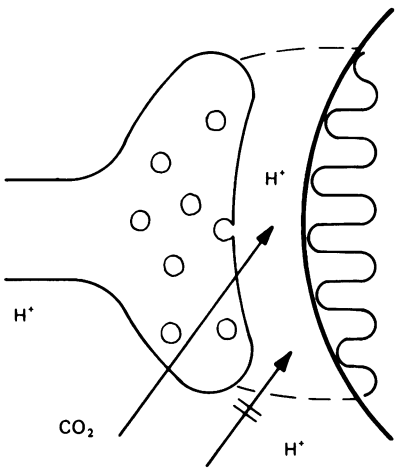


Fig. 6. Diagram showing a cholinergic synapse. The hydrogen ion concentration in the synaptic cleft modulates the cholinergic transmission perhaps by an anticholinesterase effect (Gesell & Hansen 1942, 1945). It may be speculated that the access of H^+ to the synaptic gap is prevented when the external $[H^+]$ increases.

distributed. Maximal drive of ventilation was observed in two areas, one medial to the vagal root and the other medial to the hypoglassal root but lateral to the pyramids. These two areas (rostral and caudal) were also identified by electrical stimulation (Loeschcke, de Lattre, Schlaefke & Trouth, 1970).

In the area between these two, the intermediate area, no positive ventilatory responses to acid were found, but rather a slight depression. This area has attracted much interest because either coagulation, application of procaine or cooling (to 12 °C) eliminated central chemosensitivity with the result that in a previously chemodenervated animal breathing stopped completely even during inhalation of CO_2 (Schlaefke *et al.* 1970; Schlaefke, See, Herker-See & Loeschcke, 1979*b*; Schlaefke, Kille & Loeschcke, 1979*a*; Cherniack, Euler, Homma & Kao, 1979). When the central ends of the cut peripheral chemoreceptor nerves were stimulated electrically rhythmic breathing resumed (Loeschcke, Schlaefke, See & Herker-See, 1979) indicating that the respiratory reflex centres were still functioning. But also in this case the chemosensitivity to inhaled CO_2 was lost (see fig. 5 in Loeschcke *et al.* 1979). Moreover, in awake cats surviving after elimination of both intermediate areas, with intact peripheral chemoreceptors all or most of the steady state response to inhaled CO_2 was lost indefinitely (Schläfke *et al.* 1979*a*).

It was therefore suggested that the impulse traffic from the two distinct chemo-

sensitive areas converged to the intermediate area where it could be interrupted by a small lesion or cooling. This hypothesis was supported by Dev & Loeschcke (1979*a*) (Fig. 7) who stimulated respiration by applying nicotine to the rostral or caudal areas. Application of procaine to the intermediate areas on both sides now reduced the nicotine effect almost to zero. Further information was recently provided by Milulski, Marek & Loeschcke (1982) who found that a superficial cut of the medulla close to

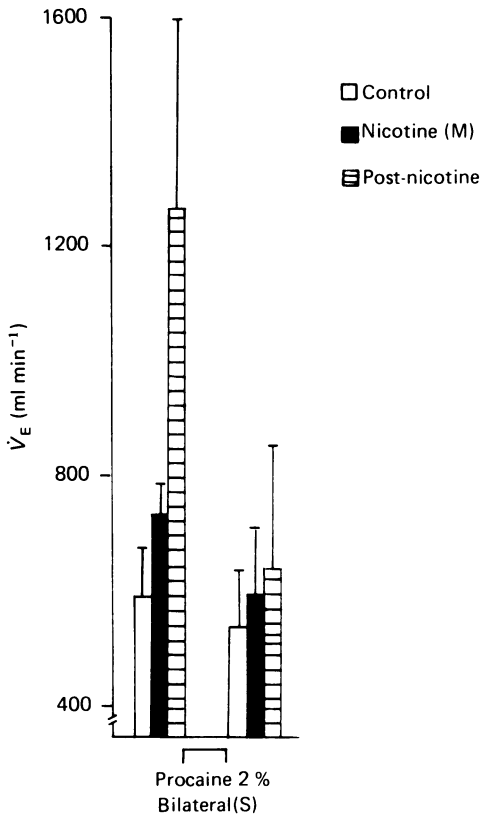


Fig. 7. Response of ventilation to nicotine applied to the rostral area before and after application of procaine to the intermediate area. Left column, control; middle column, mean of first fifteen breaths after nicotine; right column, mean of sixteen to thirty breaths after nicotine. The full nicotine effect is obvious only after fifteen breaths. Both the early and particularly the late nicotine effects are depressed by the application of procaine on the intermediate area. Dev & Loeschcke (1979*a*, *b*). Courtesy of Springer-Verlag.

the mid line in peripherally chemodenervated cats caused respiratory arrest (Fig. 8), indicating that the afferent impulse traffic is crossed.

Evoked potentials in the paragigantocellular nucleus (Taber) and in the nucleus of the solitary tract after stimulating the caudal area have been observed by Davies & Loeschcke (1977) and Davies (1980). Schlaefke, See & Burghardt (1980) have described inhibitory projections to the splanchnic nerve while Trzebski, Zielinski, Lipski & Majcherczyk (1971) and Trzebski, Zielinski Majcherczyk, Lipski & Szulczyk (1974) recorded an increased impulse activity in several sympathetic nerves after

increasing the acidity on the ventral surface. Willshaw (1975, 1977) reported an increase of efferent carotid nerve inhibitory activity after alkalinization of the medullary surface.

Stimulation of the carotid sinus nerve was still effective during cooling of the intermediate areas on both sides although the response was diminished. Some impulses from the carotid sinus nerve could, therefore, bypass the site of central

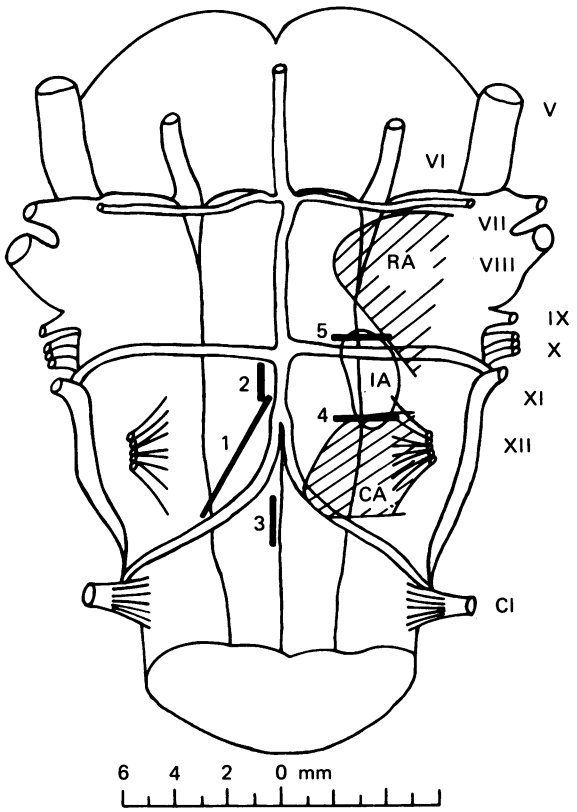


Fig. 8. Ventral aspect of the cat's medulla. The hatched areas represent the rostral and the caudal chemosensitive areas. A superficial cut near the mid line (1) abolishes most of central chemosensitivity; subsequent additional cuts (2 and 3) abolish the remainder. This indicates a complete crossing of the impulse traffic to the contralateral side. There were only relatively small diminutions of ventilation after cuts 4 and 5. Mikulski *et al.* (1981). Courtesy of Drs Mikulski and Marek.

chemosensitivity. Also direct connexions between the carotid bodies and the central chemosensitive areas have been demonstrated both by evoked potentials (Davies & Loeschcke, 1977; Davies, 1980) and by increased activity of H^+-activated neurones during sinus nerve stimulation (See & Schlaefke, 1978).

Von Euler & Söderberg (1952) were the first to observe tonically discharging neurones in an undefined location in the medulla oblongata which increased greatly in frequency during inhalation of CO_2. Later, Shimada, Trouth & Loeschcke (1969) succeeded in recording from H^+ activated neurones in the caudal area. Schlaefke,

Pokorski, See, Prill, Kille & Loeschke (1975), Cakar & Terziŏglu (1976), Prill (1977), Pokorski, Schlaefke & See (1975), Pokorski (1976) and Schlaefke (1981 (Fig. 9) showed that in all three areas and also in the underlying paragigantocellular nucleus (Taber) action potentials could be recorded when CO_2 was inhaled, and when fixed acid was either injected or superfused. Most of the neurones fired slowly but some discharged at higher frequencies, and these were used for the investigation of the effects of alkali

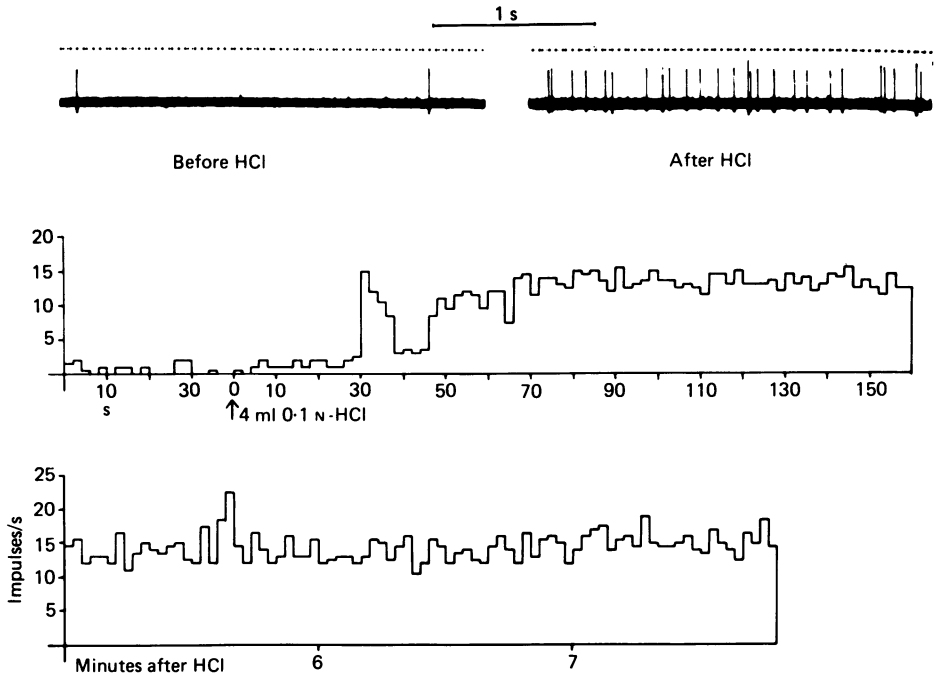


Fig. 9. Recording from a neurone in the intermediate area. The upper trace shows the discharge before and after I.V. injection of 4 ml 0·1 N-HCl. The lower traces are a continuous record of the impulse frequency before and after the injection of acid (at arrow). Schlaefke *et al.* (1975). Courtesy of *Bull. Physio-Path. Resp.*

injection. Only about 50% of the spontaneously active neurones in these regions responded to pH changes; of the remainder, some were responsive to touch of the limbs, while some could not be activated by a variety of stimuli.

It was so far not possible to maintain intracellular potentials for any reasonable time. For any given neurone the correlation between discharge frequency and pH measured locally on the medullary surface was much better than that with pH measured at any other site.

All hydrogen-ion activated neurones as far as investigated were found to be excited by acetylcholine applied electrophoretically. There were also neurones which did not react to H^+ but still responded to acetylcholine. Among these may be the candidates for the cardiovascular effects which are seen when the ventral medullary surface is stimulated. Such effects have been described by Loeschcke *et al.* (1958), Schlaefke & Loeschcke (1967) and by Feldberg (1976, 1980) and Guertzenstein (1973).

Since a pH change on the ventral surface of the medulla did not produce clear and reproducible changes of arterial pressure and heart rate it must be doubted whether the cardiovascular effects are transmitted by the chemosensitive neurones (Loeschcke, 1980). Furthermore, in some instances the respiratory and vascular responses to several drugs were found to go in the same and in others to go in the opposite direction.

Lipscomb & Boyarski (1972) were unable to record action potentials induced by application of H^+ on the ventral superficial layer of the medulla oblongata. In view of the evidence already quoted this negative finding should not be taken too seriously; the chemosensory mechanism is easily anaesthetized and it is technically difficult to maintain the position of the electrodes in such a superficial layer. The electrodes used by Schlaefke *et al.* (1975) were miniaturized which was necessary for them to 'float'. It was also found that the electrodes stayed in position much better if the penetration was made at a sharp angle to the surface, which gives them some support and friction in the relatively tough tissue of the marginal glia.

Lipscomb & Boyarski's hypothesis, that the respiratory effects of acid or temperature might be due to a transport of acidity or heat along blood vessels, should be taken seriously especially since both Trzebski, Mikulski & Przybyszewski (1980) and Shams *et al.* (1982) obtained the typical effects of acidification by injection into the vertebral arteries. However, a superfusion is not the same as an intra-arterial injection. It is scarcely possible that blood, during its passage, equilibrates completely through arterial and arteriolar walls since it is well buffered. In an arterial bulk injection, on the other hand, the blood is more or less replaced by the injected fluid. However, it is possible that some acid or some heat might enter or leave the blood from a subarachnoid perfusion and exchange it again in the deeper tissue. The heat profile published by Schlaefke & Loeschcke (1967) does not support the existence of transported heat into the interior of the medulla after spotwise cooling of the ventral surface. Also the observations of Mitchell & Herbert (1974) and Marino & Lamb (1975) that extracellular acid inhibits respiratory neurones rather than driving them speak against an effect as a central respiratory drive of transported acid.

The first cell type suspected of being chemosensitive was described by Trouth, Loeschcke & Berndt (1973*a*, *b*). Schlaefke, Kille, Folgering, Herker & See (1974) and Dermietzel (1976) presented detailed accounts of the different cell types which may be found in the chemosensitive region. It is still not clear which cells are chemosensitive. Several cell types have been found using the electron microscope (Ullah, 1973; Dermietzel, 1976; Leibstein, Willenberg & Dermietzel, 1981). There are plenty of synapses on the somata and even more on long dendrites. The distribution of cholinergic cells has been investigated by histochemical methods for acetylcholinesterase. With regard to cell type, nothing has been seen to distinguish this region from other parts of the C.N.S. except for a denser packing of cholinergic cells in the chemosensitive region (Leibstein *et al.* 1981). However, the topography of the intercellular spaces is peculiar in so far as they are relatively wide and are in open connexion with branched recesses covered by basal membrane which are open to the subarachnoid space. This type of tissue was called glia spongiosa (Dermietzel, 1976).

Fukuda & Honda (1975) and Fukuda, Honda, Schlaetke & Loeschcke (1978) succeeded in keeping slices of about 0·4 mm thickness from the ventral surface of the

rat brain alive in a perfusion chamber for hours. They were able to record intracellular potentials of up to 90 mV. The membrane potentials decreased slightly if $[H^+]$ was elevated by increasing P_{CO_2}. These cells, however, were silent and could not be stimulated electrically. They were thought to be glia cells.

Later Fukuda & Loeschcke (1977) and Fukuda, See, Schlaefke & Loeschcke (1979), working on slices from the ventral surface, also found spontaneously discharging cells. The action potentials of these cells were recorded extracellularly. Some of them were activated by H^+, while a small number were inhibited. The response of a single cell was, however, under the given condition always reproducible. The relation between discharge frequency and extracellular pH usually showed some hysteresis. Elevating $[H^+]$ above a critical level in non-respiratory acidosis caused the activity of the cell to decrease again. This observation may be the cellular homologue of the similar response of ventilation in the injection experiments of Shams *et al.* (1982). In the chemosensitive areas the majority of the cells were activated by H^+. In slices of the dorsal surface of the medulla the same types of cellular responses were observed, but here the majority of the cells were inhibited by H^+. The response of a cell activated by H^+ after treatment with a solution of reduced calcium and increased magnesium concentrations could be reversed i.e. it was now inhibited by H^+. Such behaviour is said to be indicative of a synaptic effect. These findings will play an important role in the interpretation of the chemosensitive mechanism to be presented below.

A cholinergic mechanism as a link in the chemosensitive mechanism

Mitchell, Massion, Carman & Severinghaus (1960) described an inhibition of ventilation when acetylcholine (ACh) was applied to the area postrema. Acid had, however, no effect here and so this action of ACh is no indication of chemosensitivity. However, when the same authors (Mitchell *et al.* 1963*a*, *b*) applied acetylcholine to what was later called the rostral chemosensitive areas, ventilation increases. The location of the ACh effect on ventilation and also on circulation was studied in more detail by Dev & Loeschcke (1979*a*, *b*). The topical distribution showed two peaks of maximal effect and these coincided with those of sensitivity to hydrogen ions. Also nicotine was found to mimic the effect of ACh and physostigmine enchanced its action. In later experiments by Tok & Loeschcke (1981) ventilation was found to be much depressed by Atropine and in some cases to be completely arrested with higher concentrations. Also I.V. hexamethonium exhibited a depressing action on the ACh effect. The combined effect of nicotine and procaine has already been mentioned.

Tok & Loeschcke (1981) re-investigated the effect of progesterone on ventilation. It was found that progesterone superfused onto the ventral medullary surface raised ventilation. This effect was counteracted by atropine.

This group of experiments suggests that the chemosensitive mechanism involves a cholinergic link which can be eliminated by atropine.

While Fukuda & Loeschcke (1979) were studying the *in vitro* effects of cholinergic drugs on H^+ sensitive neurones, almost identical responses were being recorded on the ventilation to the *in vivo* application of cholinergic drugs to the ventral medullary surface. ACh, like H^+, stimulated the neurones (Fig. 10) and these effects were additive. Nicotine acted similarly and so did eserine. Mecamylamine, an acetylcholine

inhibitor, stopped impulse generation (Fig. 11). The most important observation was that mecamylamine inhibited not only the effect of ACh but also that of H^+. The results with atropine were more complicated since impulse generation was not abolished and usually even increased; still the effect of H^+ was lost. This may be interpreted that atropine has a competitive action on the receptor acting in the same sense on the receptor but blocking it for H^+.

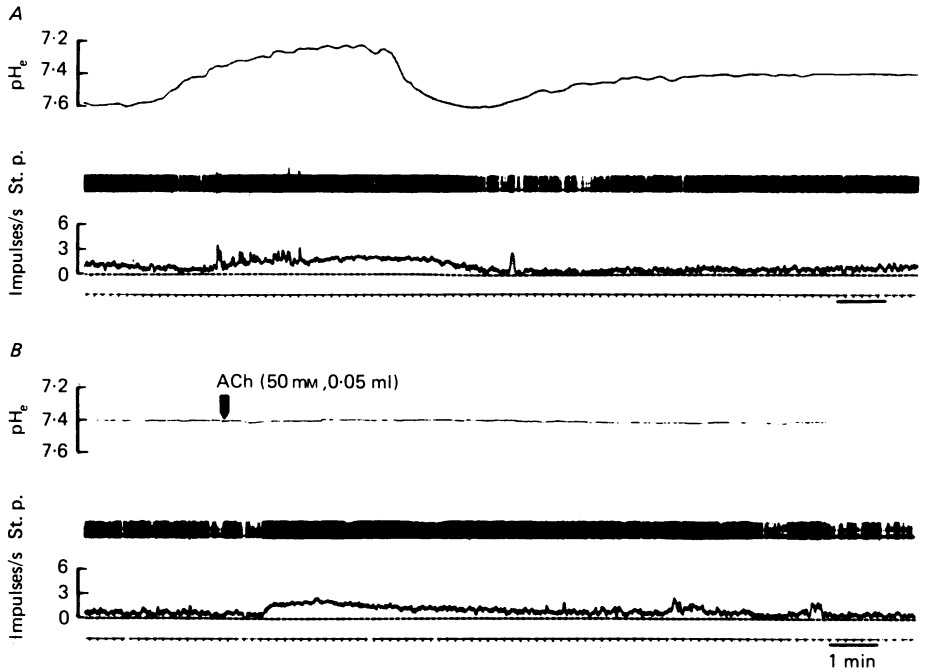


Fig. 10. *A*, effects of changes of pH on an *in vitro* preparation of a slice of the ventral medullary surface. From above are shown pH, standardized impulses (St. p.), integrated impulses. *B*, continuation of the recording. At the arrow acetylcholine was injected into the perfusate. The responses to acetylcholine mimic the effect of increased acidity. Fukuda & Loeschcke (1979). Courtesy of Springer-Verlag.

It has already been mentioned that decreases of calcium and increases of magnesium concentrations reverse H^+ sensitivity. To the extent that these effects are characteristic of synaptic transmission the over-all conclusion must be that the chemosensitive mechanism is a cholinergic synapse on which H^+ acts like ACh and can be replaced by it. Blockade is possible by mecamylamine, atropine and partly also by hexamethonium, which suggests the presence of both muscarinic *and* nicotinic receptors.

An excursion into the control of breathing in muscular exercise

If we dare carry on these arguments then a cholinergic, chemosensitive synapse would imply a synaptic neural input, on whose nature we can only speculate. There is, however, a relevant experimental finding which looks almost too good to be true (Fig. 12). Spode (1980) stimulated the ventral roots in the lumbar part of the spinal

cord. In order to avoid any kind of adaptation the stimulus was given in trains alternating between the right and the left side. A marked increase of ventilation was observed which according to Kao (1956) could be interpreted as a neural drive from the muscle. If central chemosensitivity was abolished by local cooling of the intermediate areas (in a chemodenervated animal) breathing stopped completely during rest and also during exercise and the effect was reversible. Assuming that

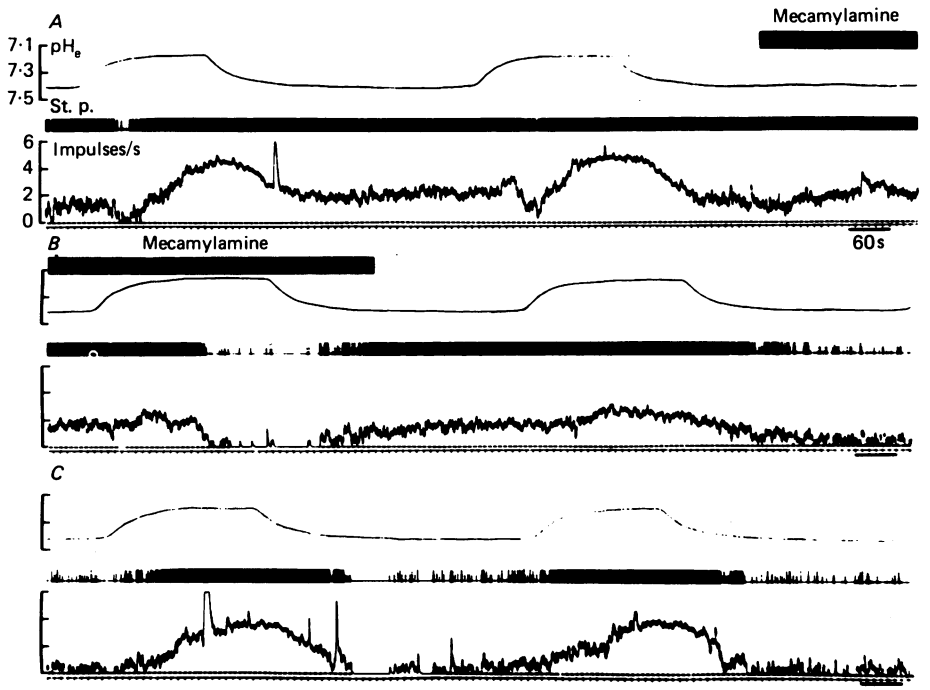


Fig. 11. Effects of increased acidity in the perfusate on an *in vitro* tissue slice of the ventral medullary surface. From above downward: pH, standardized impulses (St. p.), integrated impulses. Under the influence of mecamylamine the pH effect is abolished or even reversed. It recovers after washing out. Fukuda & Loeschcke (1979). Courtesy of Springer-Verlag.

neurogenic signals from the muscle would reach the ventral area of chemosensitivity in the form of a synaptic input the interruption of central chemosensitivity should also eliminate the propagation of the neural drive, and this is exactly what happened in this technically very difficult experiment. It could, of course, be argued that under this condition the neurogenic drive might not really have been interrupted but might only not have sufficed to drive ventilation. It is known, however, that the respiratory drive from the hypothalamus in hyperthermia does survive the elimination of the central chemosensitivity and also that the drive from peripheral chemoreceptors can maintain ventilation after elimination of the central drive.

Schlaefke, See & Kille (1979*c*) found that some neurones of the nucleus paragigantocellularis could be driven by stimulation of the tibial nerve as well as by H^+. This corroborates the idea that the neural drive in exercise is relayed in chemosensitive neurones, or in other words that H^+ modulates the transmission of neurogenic impulses related to exercise.

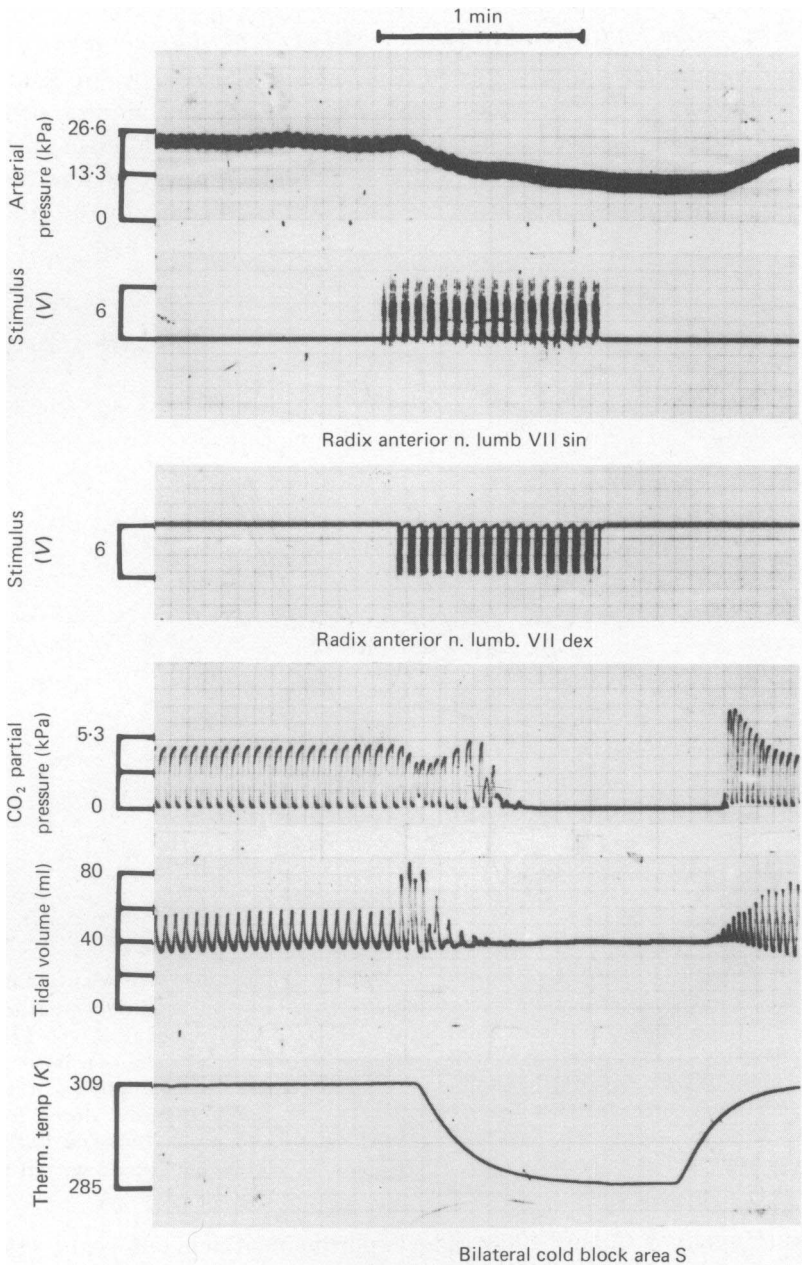


Fig. 12. Rhythmic stimulation, alternating between the left and right ventral roots (L VII). From above downward: arterial pressure, stimulation of left root, stimulation of right root, airway P_{CO_2}, tidal volume, temperature on both intermediate areas. Stimulation increases tidal volume. Bilateral cooling of the intermediate areas causes respiratory arrest in spite of continued stimulation of the ventral roots. This indicates that the increase of ventilation in exercise cannot be maintained when central chemosensitivity has been inhibited. Spode (1980). Courtesy of Dr Spode.

Generalization leading to a tentative model of respiratory chemosensitivity

A similar conclusion could be drawn from earlier experiments by Schlaefke, See, Massion & Loeschcke (1969) concerning unspecific sensory inputs such as those initiated by touching the cornea. Such inputs have a reproducible effect on ventilation, but this effect is lost during cooling of the intermediate areas. It was thought that such sensory inputs as many others would act unspecifically on the reticular

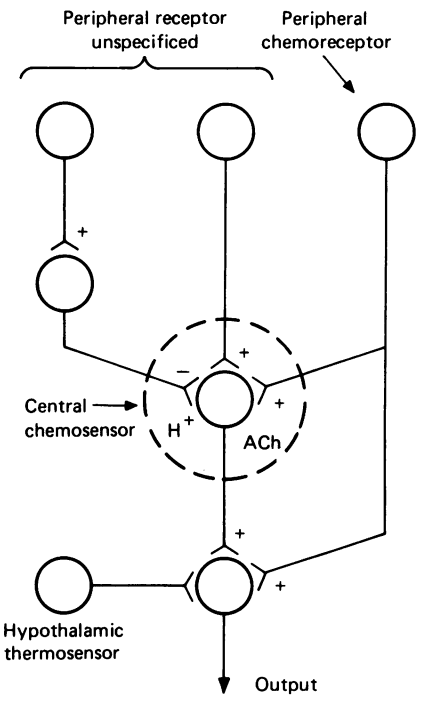


Fig. 13. Schematic diagram of central respiratory chemosensitivity with its principal interconnexions. Inhibitory and excitatory afferents both unspecific (sympathetic and fibres from the integument and from muscle) and specific fibres from the peripheral chemoreceptors are supposed to feed in synaptically to a central chemosensitive neurone. These synapses are believed to be cholinergic and may be affected by applied acetylcholine. Hydrogen ions affect the cholinergic synaptic transmission. Some fibres from the peripheral chemoreceptors bypass the region of central chemosensitivity as do the fibres from the hypothalamic thermosensor. There is a final convergence on an output neurone which drives the respiratory motoneurones.

formation (Hugelin & Cohen, 1963). The experiment of Schlaefke *et al.* (1969) is now suggesting that, probably among others, there is also a relay in the chemosensory region which mediates the respiratory effect.

An undoubtedly much simplified schematic representation of the role of central chemosensitivity in the control system is shown in Fig. 13. Inputs from muscle, the neural drive and unspecific sensory inputs are thought to converge on neurones in the chemosensitive areas driving them through cholinergic synapses. H^+ acts by modulating the synaptic transmission. The specific inputs from the peripheral chemosensors partly enter the central chemosensory structure and partly bypass it.

Finally efferents from neurones in the chemosensory areas reach the respiratory output neurones. This model rekindles the classical ideas of Gesell & Hansen (1942, 1945) about the role of acetylcholine in respiratory control.

Signal transmission

The receptor in the brain tissue responds to extracellular $[H^+]$ at least up to a certain level. The transmission from blood to the extracellular fluid need not be, and it is not the same for the three variables of the Henderson–Hasselbalch equation. There are two boundaries which have to be passed in parallel, the choroid plexus and the endothelium of the brain capillaries.

The blood flow in the choroid plexus is extremely high (Page, Funsch, Brennan & Hernandez, 1980) and the tissue volume it supplies consists of the choroid plexus tissue only. It is to be expected that the a–v CO_2 difference of plexus blood is very small. This means that the average P_{CO_2} of the choroid plexus is low, close to arterial. However, the CO_2 of the secreted plexus fluid comes into equilibrium with the CO_2 of the brain surface with which it is in contact. This makes the fluid more acid and partially explains the higher acidity of c.s.f. in comparison to blood plasma. Other ion exchanges may also occur which cannot be easily predicted and are difficult to assess. The assumption that the composition of cerebrospinal fluid in a steady state equals that of extracellular fluid is only an approximation. Free exchange between the two compartments, of course, serves to reduce the differences in composition between the two fluids. The local extracellular pH, however, is only partly under the influence of the cerebrospinal fluid because the tissue is perfused by the blood. On average, in most parts of the tissue we may assume that the local P_{CO_2} determined by the usual factors, local metabolism, CO_2 binding capacity of the blood, blood flow, and the distance to the capillaries. For the purpose of balance in a steady state it usually suffices to define an average tissue P_{CO_2}: one such proposal was that of Ponten & Siesjö (1966) who claimed that tissue P_{CO_2} equalled the algebraic means of venous and arterial P_{CO_2} of cerebral blood plus 1 torr, an approximation verified by Ahmad *et al.* (1976).

Several authors have studied the relation between $[HCO_3^-]$ in blood and in c.s.f. When plasma $[HCO_3^-]$ changes in response to acid–base changes, in the dog and man the $[HCO_3^-]$ in c.s.f. increases or decreases by only about 40 % as much as the increase or decrease in blood plasma (Pappenheimer, Fencl, Heisey & Held, 1965; Mitchell, Carman, Severinghaus, Richardson, Singer & Shnider, 1965; Kronenberg & Cain, 1968; Fencl, 1971). In cats it was even less, for example, 20 % (Ahmad *et al.* 1976). Although in cases of chronic metabolic acid–base disturbances in man this relation was maintained, it was found to be time-dependent in the cat; the increase of bicarbonate concentration in extracellular fluid (e.c.f.) after an I.V. injection or infusion of bicarbonate diminished with time to the extent that after an hour not much of the increase was left. It is now established (Leusen, 1972) that bicarbonate *does* exchange between blood plasma and e.c.f. It is now known also that the $[HCO_3^-]$ exchange between blood and brain is a fast process occurring in minutes if not in seconds (Ahmad *et al.* 1976; Ahmad & Loeschcke, 1982*c*). It has finally been shown that the exchange of HCO_3^- occurs simultaneously with an exchange of Cl^- in the opposite direction (Fig. 14). This exchange is now assumed to take place by way of a specific

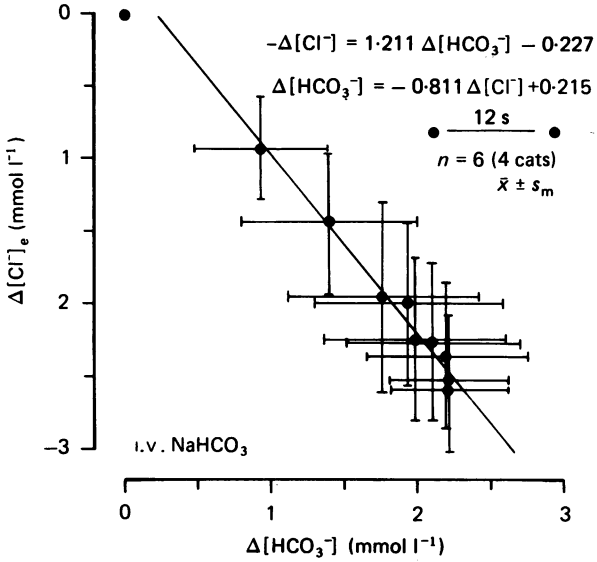


Fig. 14. Exchange of bicarbonate and Cl^- between plasma and brain extracellular fluid after I.V. injection of bicarbonate. Ahmad & Loeschcke (1982*c*). Courtesy of Springer-Verlag.

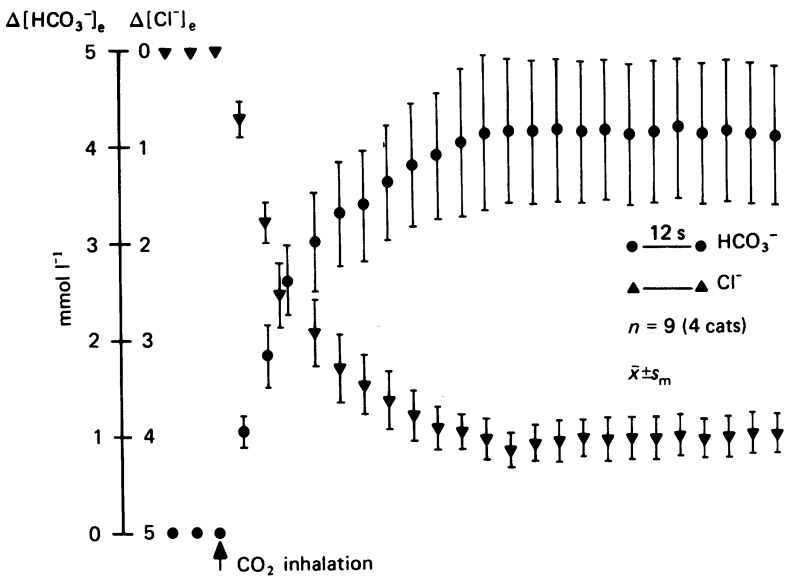


Fig. 15. Changes of bicarbonate and chloride concentrations in brain extracellular fluid during inhalation of CO_2. Ahmad & Loeschcke (1982*b*). Courtesy of Springer-Verlag.

anion exchange channel, possibly using a protein carrier (Wieth, Brahm & Funder, 1980). The exchange occurs through the endothelium of the brain capillaries.

During CO_2 inhalation the bicarbonate concentration in e.c.f. increases. This was first shown by Pannier, Weyne & Leusen (1970). The increase of $[HCO_3^-]$ in e.c.f. was greater than that in blood plasma and occurred even if, by additional infusion of acid, the bicarbonate concentration in plasma was prevented from rising or even fell. The sources of HCO_3^- in this case can only be the cells of the brain tissue. Ahmad & Loeschcke (1982*b*) showed by electrochemical methods that also in this case HCO_3^-

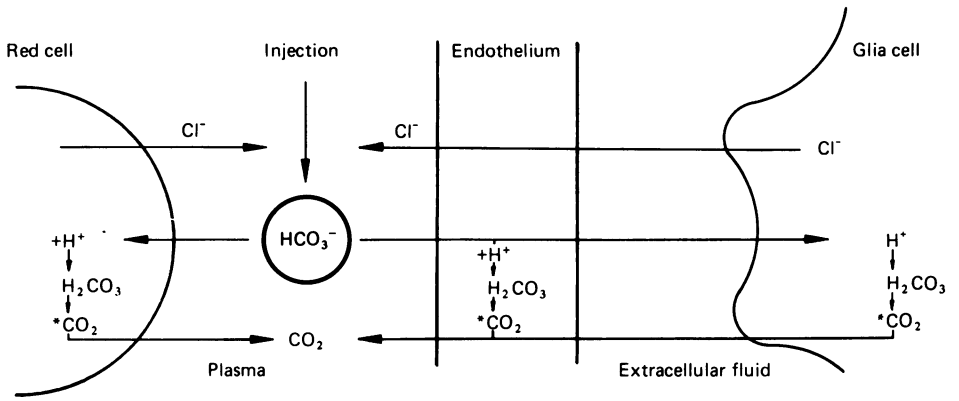


Fig. 16. Schematic diagram of the exchange processes between the five compartments: red cells, plasma, endothelium, brain extracellular fluid and brain cells (presumably glia), following I.V. injection of bicarbonate. * = carbonic anhydrase. Ahmad & Loeschcke (1981*c*). Courtesy of Springer-Verlag.

is exchanged for Cl^- in a one-to-one fashion between extracellular fluid and cells (Fig. 15). This exchange takes place in seconds and it is inhibited by stilbene derivatives.

Extracellular pH becomes a variable which depends on the two types of anion exchange between plasma and endothelium and through endothelium to the extracellular fluid and between cells and extracellular fluid. For any modelling of pH kinetics in e.c.f. all five compartments (Ahmad & Loeschcke, 1982*b*, *c*), namely red cells, plasma, endothelium, extracellular fluid and glia cells must be considered (Fig. 16). This is true for metabolic as well as respiratory acidosis. The result of such a mathematical model – as should be created – will give the quantitative answers about steady and transient states in all acid base disturbances and especially about the extracellular pH under all these conditions.

The model of Middendorf & Loeschcke (1976*a*, *b*) made use of the bicarbonate relation between plasma and c.s.f. as determined by the authors mentioned. It already approached reality reasonably well in respiratory and metabolic acidosis and could also simulate variation of the total metabolism among other features. It follows from the model that the response of ventilation to respiratory acidosis is much higher than that to metabolic acidosis. The increase of ventilation, however, is more effective in regulating blood pH in metabolic than in respirating acidosis (Middendorf, 1974, 1976*b*).

In conclusion it may be stated that the extracellular pH in the brain is the main chemical signal determining ventilation. This pH depends on the tissue P_{CO_2} and the bicarbonate concentration in the tissue. The distribution of bicarbonate between plasma and c.s.f. under given conditions can be experimentally determined. There are processes preventing a full equilibrium and any assessment of the extracellular pH should take account of the exchange processes between the five compartments: red cells, plasma, endothelium of the brain capillaries, extracellular fluid and brain cells.

REFERENCES

AHMAD, H. R., BERNDT, J. & LOESCHCKE, H. H. (1976). Bicarbonate exchange between blood, brain extracellular fluid and brain cells at maintained P_{CO_2}. In *Acid Base Homeostasis of the Brain Extracellular Fluid and the Respiratory Control System*, ed. LOESCHCKE, H. H. pp. 19–27. Stuttgart: Thieme Verlag.

AHMAD, H. R. & LOESCHCKE, H. H. (1982*a*). Transient and steady state response of pulmonary ventilation to the medullary extracellular pH. *Pflügers Arch.* (submitted).

AHMAD, H. R. & LOESCHCKE, H. H. (1982*b*). Fast bicarbonate–chloride exchange between brain cells and brain extracellular fluid in respiratory acidosis. *Pflügers Arch.* (submitted).

AHMAD, H. R. & LOESCHCKE, H. H. (1982*c*). Fast HCO_3^-–Cl^- exchange between plasma and brain extracellular fluid at maintained P_{CO_2}. *Pflügers Arch.* (submitted).

ÅSTRÖM, A. (1952). On the action of combined carbon dioxide excess and oxygen deficiency in the regulation of breathing. *Acta physiol. scand.* **27**, suppl. 98.

BENZINGER, T., OPITZ, E. & SCHOEDEL, W. (1938). Atmungserregung durch Sauerstoffmangel. *Pflügers Arch.* **241**, 71–77.

CAKAR, L. & TERZIOĞLU, M. (1976). The response of the chemosensitive areas of the cat to the breathing of hypercapnia gas mixtures. *Bull. Physio-path. Resp.* **12**, 224 pp.

CHERNIACK, N. S., VON EULER, C., HOMMA, I. & KAO, F. F. (1979). Graded changes in central chemoreceptor input by local temperature changes on the ventral surface of the medulla. *J. Physiol.* **287**, 191–211.

CRAGG, P., PATTERSON, L. & PURVES, M. J. (1977).The pH of brain extracellular fluid in the cat. *J. Physiol.* **272**, 137–166.

DAVIES, R. O. (1980). Evidence that neural paths from the caudal and cranial chemoreceptor zones of the ventral medulla converge in the intermediate zone. *Proc. int. Union physiol. Sci.* **XIV**, 371.

DAVIES, R. O. & LOESCHCKE, H. H. (1977). Neural activity evoked by electrical stimulation on the chemosensitive areas on the ventral medullary surface. *Proc. int. Union physiol. Sci.* **XIII**, 164.

DERMIETZEL, R. (1976). Central chemosensitivity, morphological studies. In *Acid-Base Homeostasis of the Brain Extracellular Fluid and the Respiratory Control System*, ed. LOESCHCKE, H. H. pp. 52–65. Stuttgart: Thieme Verlag.

DEV, N. B. & LOESCHCKE, H. H. (1979*a*). Topography of the respiratory and circulatory responses to acetylcholine and nicotine on the ventral surface of the medulla oblongata. *Pflügers Arch.* **379**, 19–27.

DEV, N. B. & LOESCHCKE, H. H. (1979*b*). A cholinergic mechanism involved in the respiratory chemosensitivity. *Pflügers Arch.* **379**, 29–36.

VON EULER, C. & SÖDERBERG, U. (1952). Medullary chemosensitive receptors. *J. Physiol.* **118**, 545–559.

FELDBERG, W. (1976). The ventral surface of the brainstem: a scarcely explored region of pharmacological sensitivity. *Neuroscience* **1**, 427–441.

FELDBERG, W. (1980). Cardiovascular effects of drug acting on the ventral surface of the brain stem. In *Central Interaction between Respiratory and Cardiovascular Control System*, ed. KOEPCHEN, H. P., HILTON, S. M. & TRZEBSKI, A., pp. 45–55. Berlin, Heidelberg, New York: Springer.

FENCL, V. (1971). Distribution of H^+ and HCO_3^- in cerebral fluids. In *Ion Homeostasis of the Brain*. Alfred Benzon Symposium III, ed. SIESJÖ, B. K., SØRENSEN, S. C., pp. 175–185. Copenhagen: Munksgaard.

FENCL, V., MILLER, T. B. & PAPPENHEIMER, J. R. (1966). Studies on the respiratory response to disturbance of acid-base balance, with deductions concerning the ionic composition of cerebral interstitial fluid. *Am. J. Physiol.* **210**, 459–472.

FUKUDA, Y. & HONDA, Y. (1975). pH sensitive cells at ventrolateral surface of the rat medulla oblongata. *Nature, New. Biol.* **256**, 317–318.

FUKUDA, Y., HONDA, Y., SCHLAEFKE, M. E. & LOESCHCKE, H. H. (1978). Effect of H^+ on the membrane potential of silent cells in the ventral and dorsal surface layer of the rat medulla *in vitro*. *Pflügers Arch.* **376**, 229–235.

FUKUDA, Y. & LOESCHCKE, H. H. (1977). Effect of H^+ on spontaneous neuronal activity in the surface layer of the rat medulla oblongata. *Pflügers Arch.* **371**, 125–134.

FUKUDA, Y. & LOESCHCKE, H. H. (1979). A cholinergic mechanism involved in the neuronal excitation by H^+ in the respiratory chemosensitive structures on the ventral medulla oblongata of rats *in vitro*. *Pflügers Arch.* **379**, 125–135.

FUKUDA, Y., SEE, W. R., SCHLAEFKE, M. E. & LOESCHCKE, H. H. (1979). Chemosensitivity and rhythmic activity of neurons in the ventral surface layer of the rat medulla oblongata *in vitro* and *in vivo*. *Pflügers Arch.* **379**, R50.

GESELL, R. & HANSEN, E. T. (1942). Eserine, acetylcholine, atropine and nervous integration. *Am. J. Physiol.* **139**, 371–385.

GESELL, R. & HANSEN, E. T. (1945). Anticholinesterase activity of acid as a biological instrument of nervous integration. *Am. J. Physiol.* **144**, 126–163.

GRAY, J. S. (1950). *Pulmonary ventilation and its physiological regulation*. Springfield, IL: Springfield.

GUERTZENSTEIN, P. G. (1973). Blood pressure effects obtained by drugs applied to the ventral surface of the brain. *J. Physiol.* **229**, 395–408.

HORI, T., ROTH, G. I. & YAMAMOTO, W. S. (1970). Respiratory sensitivity of rat brain-stem to chemical stimuli. *J. appl. Physiol.* **28**, 721–724.

HUGELIN, A. & COHEN, M. I. (1963). The reticular activating system and respiratory regulation in the cat. *Ann. N.Y. Acad. Sci.* **109**, 568–603.

KAO, F. F. (1956). Regulation of Respiration during muscular activity. *Am. J. Physiol.* **185**, 145–151.

KRONENBERG, R. S. & CAIN, S. M. (1968). Effects of acetazolamide and hypoxia on cerebrospinal fluid bicarbonate. *J. appl. Physiol.* **24**, 17–20.

LAMBERTSEN, C. J., SEMPLE, S. J. G., SMITH, M. G. & GELFAND, R. (1961). H^+ and P_{CO_2} as chemical factors in respiratory and cerebral circulatory control. *J. appl. Physiol.* **16**, 473–484.

LEIBSTEIN, A. G., WILLENBERG, I. & DERMIETZEL, R. (1981). Untersuchung zur Transmittercharakteristik von Neuronen an der ventralen Oberfläche der Medulla oblongata. *Verh. anat. Ges., Jena* **75** (in the Press).

LEUSEN, I. (1954*a*). Chemosensitivity of the respiratory center. Influence of CO_2 in the cerebral ventricles on respiration. *Am. J. Physiol.* **176**, 39–44.

LEUSEN, I. (1954*b*). Chemosensitivity of the respiratory center. Influence of changes of H^+ and total buffer concentrations in the cerebral ventricles on respiration. *Am. J. Physiol.* **176**, 45–51.

LEUSEN, I. (1972). Regulation of CSF composition with reference to breathing. *Physiol. Rev.* **52**, 1–56.

LIPSCOMB, W. T. & BOYARSKI, L. L. (1972). Neurophysiological investigations of medullary chemosensitive areas of respiration. *Resp. Physiol.* **16**, 362–376.

LOESCHCKE, H. H. (1969). On specificity of CO_2 as a respiratory stimulus. *Bull. Physio-path. Resp.* **5**, 13–25.

LOESCHCKE, H. H. (1973). The respiratory control system: Analysis of steady state solutions for metabolic and respiratory acidosis-alkalosis and increased metabolism. *Pflügers Arch.* **341**, 23–42.

LOESCHCKE, H. H. (1980). Introduction. In *Central Interaction between Respiratory and Cardiovascular Control System*, ed. KOEPCHEN, H. P., HILTON, S. M., TRZEBSKI, A., pp. 45–46. Berlin, Heidelberg, New York: Springer.

LOESCHCKE, H. H., KOEPCHEN, H. P. & GERTZ, K. H. (1958). Über den Einflub von Wasserstoffionenkonzentration und CO_2-Druck im Liquor cerebrospinalis auf die Atmung. *Pflügers Arch.* **266**, 565–585.

LOESCHCKE, H. H., DE LATTRE, J., SCHLAEFKE, M. E. & TROUTH, C. O. (1970). Effects on respiration and circulation of electrically stimulating the ventral surface of the medulla oblongata. *Resp. Physiol.* **10**, 184–197.

LOESCHCKE, H. H., SCHLAEFKE, M. E., SEE, W. R. & HERKER-SEE, A. (1979). Does CO_2 act on the respiratory centers? *Pflügers Arch.* **381**, 249–254.

LOESCHCKE, H. H. & SUGIOKA, K. (1969). pH of cerebrospinal fluid in the cisterna magna and on the surface of the choroid plexus of the 4th ventricle and its effect on ventilation in experimental disturbances of acid-base-balance. *Pflügers Arch.* **312**, 161–188.

MARINO, P. L. & LAMB, T. W. (1975). Effects of CO_2 and extracellular H^+ iontophoresis on single cell activity in the cat brainstem. *J. appl. Physiol.* **38**, 688–695.

MIDDENDORF, T. (1974). Analysis of the efficiency of the respiratory control system. In *Central Rhythmic and Regulation*, ed. UMBACH, W. & KOEPCHEN, H. P., pp. 117–120. Stuttgart: Hippokrates.

MIDDENDORF, T. & LOESCHCKE, H. H. (1976*a*). Mathematische Simulation des Respirationssystems. *J. math. Biol.* **3**, 149–177.

MIDDENDORF, T. & LOESCHCKE, H. H. (1976*b*). Analysis of the respiratory control system. In *Acid-Base Homeostasis in the Brain Extracellular Fluid and the Respiratory Control System*. ed. LOESCHCKE, H. H., pp. 190–201. Stuttgart: Thieme Verlag.

MIKULSKI, A., MAREK, W. & LOESCHCKE, H. H. (1981). Interconnections between central chemosensitive areas, 'respiratory centers' and efferent output. *Pflügers Arch.* **389** (suppl.) R34.

MITCHELL, R. A., CARMAN, C. J., SEVERINGHAUS, J. W., RICHARDSON, B. W., SINGER, M. M. & SHNIDER, S. (1965). Stability of cerebrospinal fluid pH in chronic acid-base disturbances in blood. *J. appl. Physiol.* **20**, 443–452.

MITCHELL, R. A. & HERBERT, D. A. (1974). Synchronized high frequency synaptic potentials in medullary respiratory neurons. *Brain Res.* **75**, 350–355, 1974.

MITCHELL, R. A., LOESCHCKE, H. H., MASSION, W. H. & SEVERINGHAUS, J. W. (1963*a*). Respiratory responses mediated through superficial chemosensitive areas on the medulla. *J. appl. Physiol.* **18**, 523–533.

MITCHELL, R. A., LOESCHCKE, H. H., SEVERINGHAUS, J. W., RICHARDSON, B. W. & MASSION, W. H. (1963*b*). Regions of respiratory chemosensitivity on the surface of the medulla. *Ann. N.Y. Acad. Sci.* **109**, 661–681.

MITCHELL, R. A., MASSION, W., CARMAN, C. T. & SEVERINGHAUS, J. W. (1960). 4th ventricle respiratory chemosensitivity and the area postrema. *Fedn Proc.* **19**, 374.

NIELSEN, M. (1936). Untersuchungen über die Atmungsregulation beim Menschen. *Skand. Arch. Physiol.* **74**, suppl. **10**, 83–208.

PAGE, R. B., FUNSCH, D. I., BRENNAN, R. W. & HERNANDEZ, M. J. (1980). Choroid plexus blood flow in the sheep. *Brain Res.* **197**, 532–537.

PANNIER, J. C., WEYNE, J. & LEUSEN, I. (1970). The CSF/blood potential and the regulation of the bicarbonate concentration of CSF during acidosis in the cat. *Life Sci., Oxford* 287–300.

PAPPENHEIMER, J. R. (1967). The ionic composition of cerebral extracellular fluid and its relation to control of breathing. *Harvey Lectures* **61**, 71–94.

PAPPENHEIMER, J. R., FENCL, V., HEISEY, S. R. & HELD, D. (1965). Role of cerebral fluids in control of respiration as studied in unanaesthetized goats. *Am. J. Physiol.* **208**, 436–450.

POKORSKI, M. (1976). Neurophysiological studies on central chemosensor in medullary ventrolateral areas. *Am. J. Physiol.* **230**, 1288–1295.

POKORSKI, M., SCHLAEFKE, M. E. & SEE, W. R. (1975). Neurophysiological studies on the central chemosensitive mechanism. *Pflügers Arch.* **355**, R33.

PONTEN, U. & SIESJÖ, B. K. (1966). Gradients of CO_2 tension in the brain. *Acta physiol. scand.* **67**, 129–140.

PRILL, R. K. (1977). Das Verhalten von Neuronen des caudalen chemosensiblen Feldes in der Medulla oblongata der Katze gegenüber intravenösen Injektionen von $NaHCO_2$ und HCl. Thesis. Abt. Naturwiss. Med., Ruhr-Universität Bochum.

SCHLAEFKE, M. E. (1981). Central chemosensitivity – a respiratory drive. *Rev. Physiol. Biochem. Pharmac.* **90**, 171–244.

SCHLAEFKE, M. E., KILLE, J., FOLGERING, H., HERKER, A. & SEE, W. R. (1974). Breathing without central chemosensitivity. In *Central Rhythmic and Regulation*, ed. UMBACH, W., & KOEPCHEN, H. P., pp. 97–104. Stuttgart: Hippokrates.

SCHLAEFKE, M. E., KILLE, J. F. & LOESCHCKE, H. H. (1979*a*). Elimination of central chemosensitivity by coagulation of a bilateral area on the ventral medullary surface in awake cats. *Pflügers Arch.* **378**, 231–241.

SCHLAEFKE, M. E. & LOESCHCKE, H. H. (1967). Lokalisation eines an der Regulation von Atmung und Kreislauf beteiligten Gebietes an der ventralen Oberfläche der Medulla oblongata durch Kälteblockade. *Pflügers Arch.* **297**, 201–220.

SCHLAEFKE, M. E., POKORSKI, M., SEE, W. R., PRILL, R. K., KILLE, J. F. & LOESCHCKE, H. H. (1975). Chemosensitive neurons on the ventral medullary surface. *Bull. Physio-path. Resp.* **11**, 277–284.

SCHLAEFKE, M. E., SEE, W. R. & BURGHARDT, F. (1980). Influence of central chemosensitivity upon respiratory and sympathetic efferent pathways. *Neurosci. Lett.* suppl. **5**, 140.

SCHLAEFKE, M. E., SEE, W. R., HERKER-SEE, A. & LOESCHCKE, H. H. (1979*b*). Respiratory responses to hypoxia and hypercapnia after elimination of central chemosensitivity. *Pflügers Arch.* **381**, 241–248.

SCHLAEFKE, M. E., SEE, W. R. & KILLE, J. F. (1979*c*). Origin and afferent modification of respiratory drive from ventral medullary areas. In *Central Nervous Control Mechanisms in Breathing*, ed. VON EULER, C. & LAGERCRANTZ, H., pp. 25–34. Oxford: Pergamon Press.

SCHLAEFKE, M. E., SEE, W. R. & LOESCHCKE, H. H. (1970). Ventilatory response to alterations of H^+-ion concentration in small areas of the ventral medullary surface. *Resp. Physiol.* **10**, 198–212.

SCHLAEFKE, M. E., SEE, W. R., MASSION, W. H. & LOESCHCKE, H. H. (1969). Die Rolle 'spezifischer' und 'unspezifischer' Afferenzen für den Antrieb der Atmung, untersucht durch Reizung und Blockade von Afferenzen an der decerebrierten Katze. *Pflügers Arch.* **312**, 189–205.

SEE, W. R. & SCHLAEFKE, M. E. (1978). The influence of sinus nerve stimulation on neuronal activity of ventral medullary neurones. *Neurosci. Lett.*, suppl. **1**, 519.

SHAMS, H., AHMAD, H. R. & LOESCHCKE, H. H. (1981). The dependence of ventilation on H^+-activity in the extracellular fluid of the brain in respiratory or metabolic acidosis. *Pflügers Arch.* **389**, R53.

SHIMADA, K., TROUTH, C. O., LOESCHCKE, H. H. (1969). Von der H^+-Ionenkonzentration des Liquors abhängige Aktivität von Neuronen im Gebiet der chemosensiblen Zonen der Medulla oblongata. *Pflügers Arch.* **312**, R55.

SPODE, R. (1980). Ausschaltung der zentralen und peripheren chemosensiblen Atemantriebe bei der anaesthesierten Katze während Muskelarbeit. Thesis. Abt. Nat. Med., Ruhr-Universität Bochum.

TOK, T. & LOESCHCKE, H. H. (1981). Unterschung über die zentrale Wirkung von Progesteron auf die Atmung und Vasomotorik bei Katzen. *Z. Atemwegs- u Lungenkranheiten* **7**, 148–153.

TROUTH, C. O., LOESCHCKE, H. H. & BERNDT, J. (1973*a*). A superficial substrate on the ventral surface of the medulla oblongata influencing respiration. *Pflügers Arch.* **339**, 135–152.

TROUTH, C. O., LOESCHCKE, H. H. & BERNDT, J. (1973*b*). Histological structures in the chemosensitive regions on the ventral surface of the cat's medulla oblongata. *Pflügers Arch.* **339**, 171–183.

TRZEBSKI, A., MIKULSKI, A. & PRZYBYSZEWSKI, A. (1980). Effects of stimulation of chemosensitive areas by superfusion on ventral medulla and by infusion into vertebral artery of chemical stimuli in non-anaesthetized 'encaphale isole' preparation in cats. In *Central Interaction Between Respiratory and Cardiovascular Control Systems*, ed. KOEPCHEN, H. P., HILTON, S. & TRZEBSKI, A. Berlin, Heidelberg, New York: Springer.

TRZEBSKI, A., ZIELINSKI, A., LIPSKI, J. & MAJCHERCZYK, S. (1971). Increase of sympathetic preganglionic discharges and of the peripheral resistance following stimulation by H^+ ions of the superficial chemosensitive areas in the medulla oblongata in cats. *Proc. int. Union physiol. Sci.* **9**, 571.

TRZEBSKI, A., ZIELINSKI, A., MAJCHERCZYK, S., LIPSKI, J. & SZULCZYK, P. (1974). Effect of chemical stimulation and depression on the medullary superficial areas on the respiratory motoneurone discharges, sympathetic activity and efferent control of carotid area receptors. In *Central Rhythmic and Regulation*, UMBACH, W. & KOEPCHEN, H. P., pp. 170–177. Stuttgart: Hippokrates.

ULLAH, Z. (1973). Elektronenmikroskopische Untersuchungen über ein chemosensibles Areal für die Atmungsregulation im Bereich der Medulla oblongata der Hauskatze. Thesis Abt. Theoretische Medizin, G. H. Essen.

WIETH, J. O., BRAHM, J. & FUNDER, J. (1980). Transport and interactions of anions and protons in the red blood cell membrane. *Ann. N.Y. Acad. Sci.* **341**, 394–418.

WILLSHAW, P. (1975). Sinus nerve efferents as a link between central and peripheral chemoreceptors. In *The Peripheral Arterial Chemoreceptors*, ed. PURVES, M. T., pp. 253–268. Cambridge University Press.

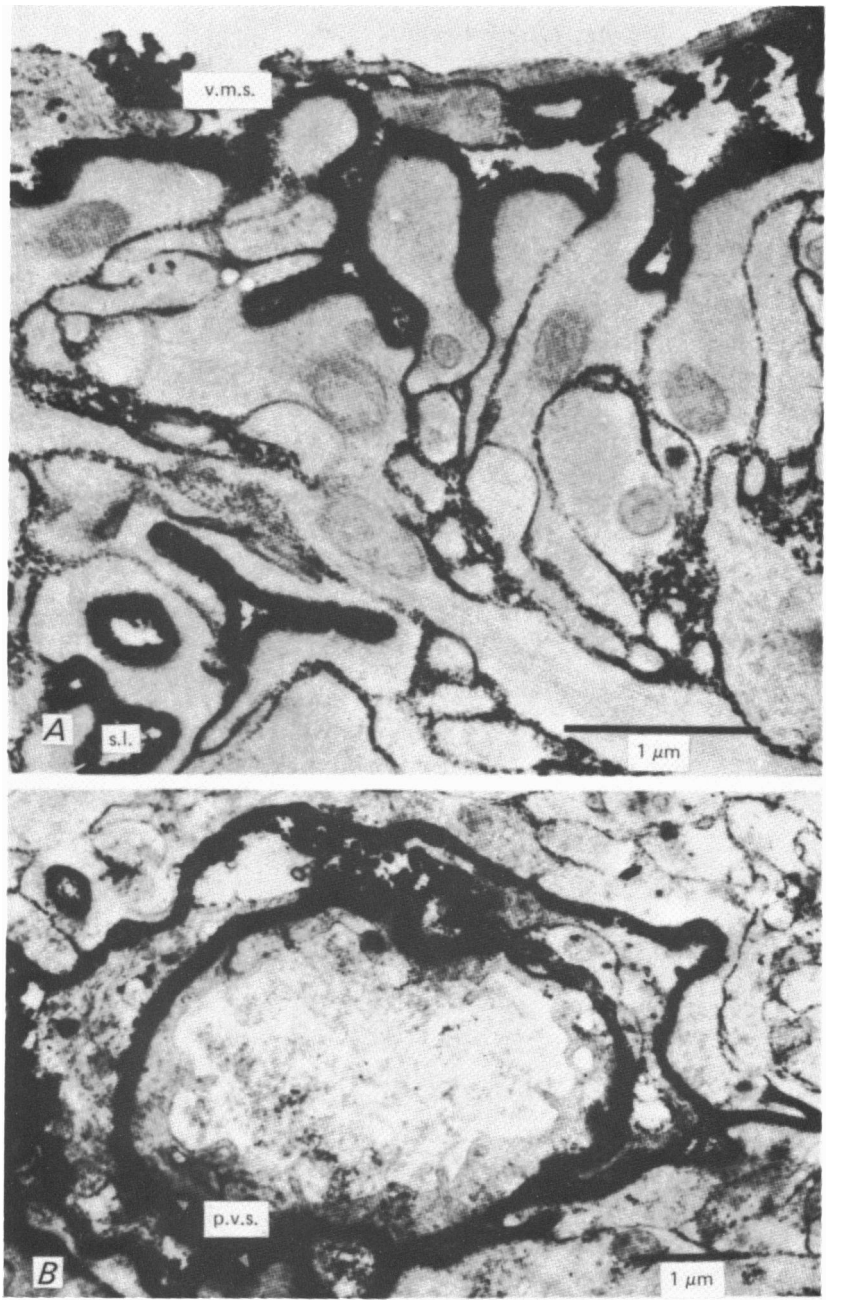
WILLSHAW, P. (1977). Mechanism of inhibition of chemoreceptor activity by sinus nerve efferents. In *Chemoreception in the Carotid Body*, ed. ACKER, H., FIDONE, S., PALLOT, D., EYZAGUIRRE, C. & LÜBBERS, D. W. pp. 168–172. Berlin, Heidelberg, New York: Springer.

WINTERSTEIN, H. (1911). Die Regulierung der Atmung durch das Blut. *Pflügers Arch.* **138**, 167–184.

WINTERSTEIN, H. (1956). Chemical control of pulmonary ventilation. III. The reaction theory of respiratory control. *New Engl. J. Med.* **255**, 331–337.

EXPLANATION OF PLATE

A, distribution of horseradish peroxidase into the extracellular space of the ventral medullary surface (v.m.s.). The marker was applied to the subarachnoid space of an anaesthetized cat. *B*, distribution of marker in perivascular space (p.v.s.) surrounding a capillary. Dermietzel (1976). Courtesy of Thieme-Verlag.


v.m.s.
A
s.l.
1 μm
p.v.s.
B
1 μm